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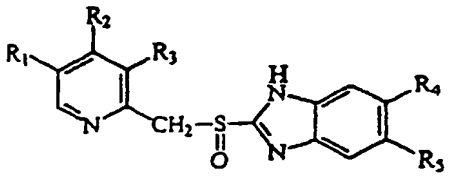
(54) Title: NEW METHOD FOR THE PREPARATION OF THE ANTI-ULCER COMPOUNDS OMEPRAZOLE, LANSOPRAZOLE AND PANTOPRAZOLE



(57) Abstract: The present invention describes a new process for the preparation of omeprazole, lansoprazole and pantoprazole of formula (XXI), (XXXIII), and which involves the formation of pyridines N-oxide using a rhenium compound as a catralyst, followed by nitration of the 4-position with nitric acid fuming in presence of a claycop. The chlorination of the 2-methyl group of pyridine was achieved by using the $POCl_3/Et_3N$, which allowed the preparation of the derivates 2-chloromethylpyridines in only one step. These derivates reacted with the mercaptobenzimidazolic derivatives in presence of ultra-sonic radiation, giving the thioethers. The oxidation of these thioethers was done with several oxidizing agents and the required anti-ulcer compounds were obtained after the substitution of nitro group by the corresponding OR groups.

DESCRIPTION

New method for the preparation of the anti-ulcer compounds omeprazole, lansoprazole and pantoprazole.

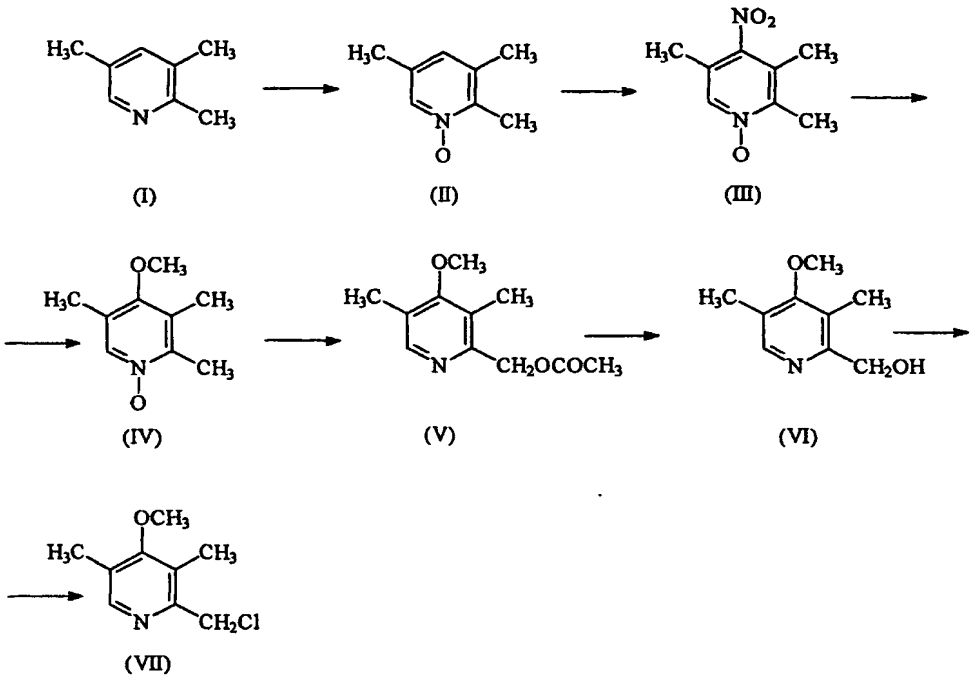
1. Field of the Invention

Chemical industry and pharmaceuticals.

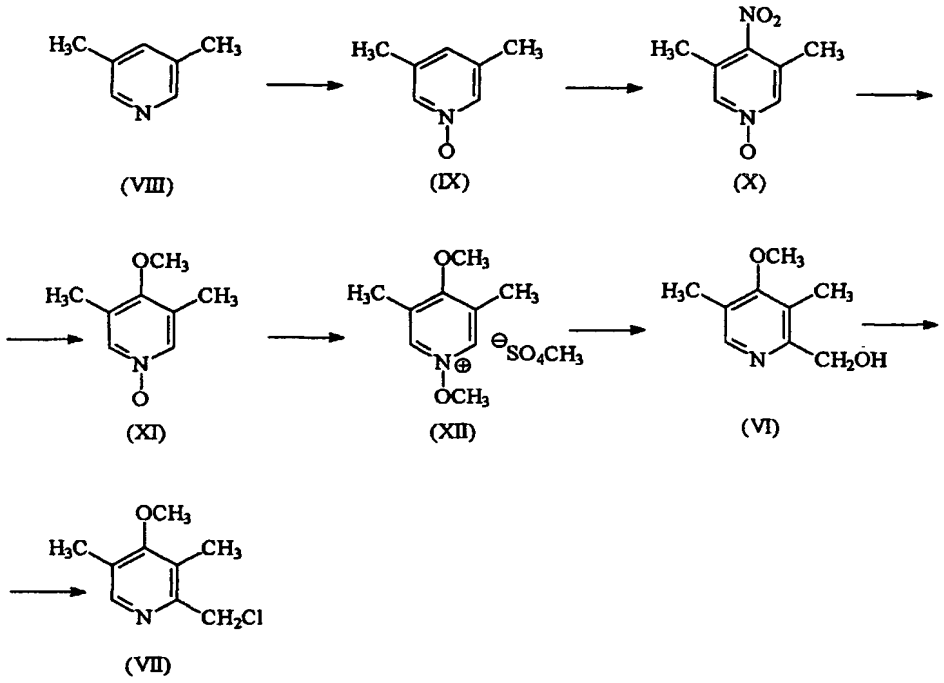
2. Background of the Invention

The synthesis of the compounds omeprazole (XXI), lansoprazole (XXXIII) and pantoprazole (XXXIV) involves the formation of a thioether through the reaction of a 2-chloromethylpyridine derivative and a mercaptobenzimidazolic compound, followed by the oxidation of the corresponding sulfoxide.

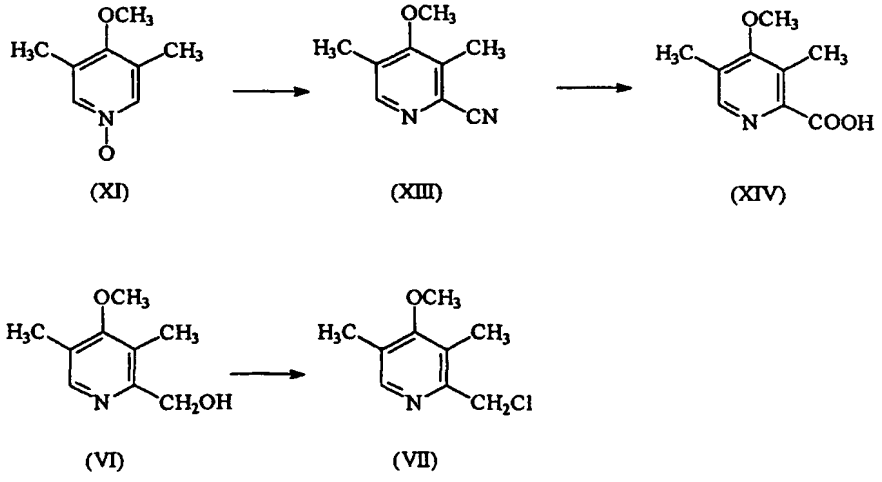
In the case of the omeprazole, there are essentially four routes for the preparation of the pyridine derivative. The first route has the 2,3,5-colidine (I) as start product and it involves the formation of the corresponding *N*-oxide (II), followed by the nitration and posterior methoxylation of the 4 position. The chlorination of the 2-methyl group of the compound (IV) was achieved by acetylation, followed of hydrolysis to the corresponding alcohol (VI) and finally chlorination (U.S. Patent 4,544,750 and European Patent 0103553 B1).



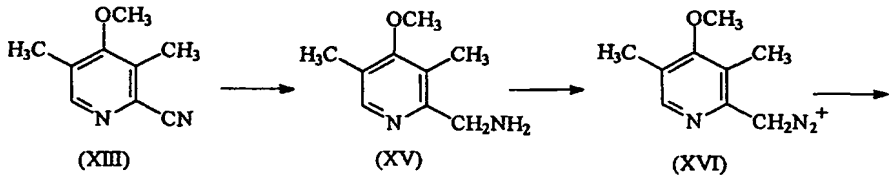
The second route has the 3,5-lutidine (VIII) as start product. This synthetic route also involves the formation of the *N*-oxide (IX), followed by nitration and methoxylation of the 4 position, yielding the 3,5-dimethyl-4-methoxypyridine *N*-oxide (XI). From this chemical intermediate, we can prepare the 2-chloromethyl-3,5-dimethyl-4-methoxypyridine (VII) by two different ways. The first one involves the methylation of the *N*-oxide, followed by the introduction of the hydroxymethyl radical, yielding the alcohol (VI) and later chlorination (U. S. Patent 4,544,750 and European Patent 0103553 B1).

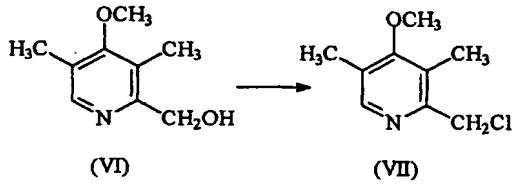


The third route consists in the preparation of the compound 3,5-dimethyl-4-methoxypyridin-2-carbonitrile (XIII), which is hydrolyded afterwards to the corresponding acid (XIV) and posteriorly reduced to the alcohol (VI). After chlorination it is possible to obtain the derivate 2-chloro-3,5-dimethyl-4-methoxypyridine (VII) (Spain Patent 2035767).



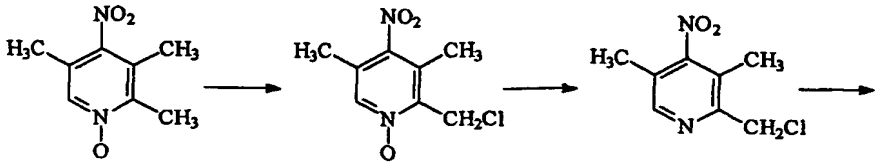
The CN group can also be reduced by hydrogenation to the corresponding amino group, yielding the compound (XV), followed by diazotization, hydrolysis to the alcohol (VI) and chlorination (German Patent 3,840,372 and European Patent 369,208).



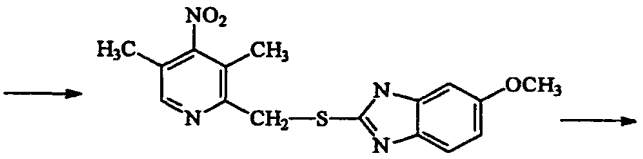


The fourth route provides the chlorination of the 2-methyl group of the nitro derivate (III), yielding the 2-chloromethyl-3,5-dimethyl-4-nitropyridine *N*-oxide (XVII), which is deoxygenated afterwards, giving the compound (XVIII) and later reacted with derivate mercaptobenzimidazolic before the substitution of nitro group by the methoxyl group (European Patent 0484265 A1).

The preparation of these anti-ulcers through the synthetic routes reported previously has the disadvantage of involving as last reaction step the oxidation of the thioether in acid conditions that lead to the decomposition of these compounds.



(III) (XV) (XVI)



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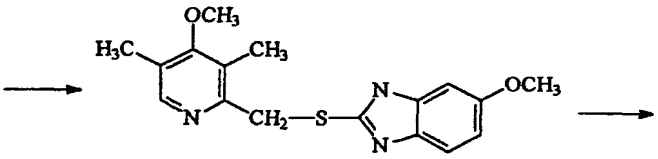
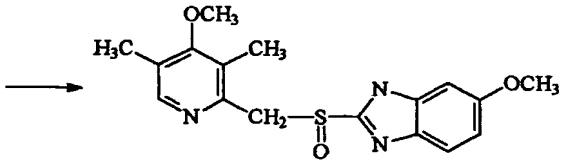


(XVIII)



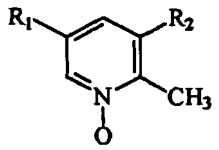
(XIX)

3. Detailed description of the invention

The present invention describes a new route for the preparation of the anti-ulcer compounds omeprazole (XXI), lansoprazole (XXXIII) and lansoprazole (XXXIV). This route involves six reaction steps, reducing some steps in the synthetic sequences reported above, which normally consist in 8-10 reactions. This new synthetic route is exemplified in the following scheme for the preparation of the omeprazole.

The innovative aspects that characterize this invention have to do with the following reaction steps:

1st The preparation of the pyridine *N*-oxides (II), (XXIII) and (XXIV) with hydrogen peroxide or *tert*-butyl hydroperoxide as oxidizing agents and a organotrioxorhenium compound as a catalyst, which made possible to simplify and to improve the method for oxidation of pyridines, normally used the reaction with hydrogen peroxide and acetic acid at 90 °C. This method is also quicker and makes it possible to obtain the *N*-oxides at room temperature with good yields. By this methods were prepared the pyridine *N*-oxides (II), (XXIII) e (XXIV).

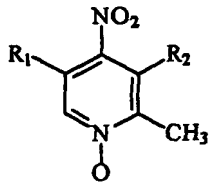


(II) $R_1 = CH_3$, $R_2 = CH_3$

(XXIII) $R_1 = H$, $R_2 = CH_3$

(XXIV) $R_1 = H$, $R_2 = OCH_3$

2nd The nitration of the *N*-oxides (II), (XXIII) and (XXIV) at 4-position using nitric acid fuming and acetic anhydride in presence or absence of claycop, with or without apolar organic solvent, has the advantage of allowing the preparation of the compounds (III), (XXV) and (XXVI) at room temperature with good yields.

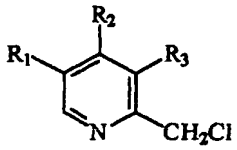


(III) $R_1 = CH_3$, $R_2 = CH_3$

(XXV) $R_1 = H$, $R_2 = CH_3$

(XXVI) $R_1 = H$, $R_2 = OCH_3$

3rd The chlorination of the 2-methyl group of pyridines *N*-oxide containing a nitro, chloro, bromo, iodo group at 4-position, with the system $POCl_3$ / Et_3N allowed the chlorination of the methyl group and the deoxygenation of the *N*-oxide in only one step in good yield, simplifying the synthesis of the chlorides (XVIII), (XXVII) and (XXVIII). The chlorination of the methyl groups through the methods reported above involves 2-5 reaction steps.

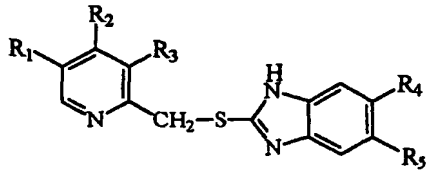


(XVIII) $R_1 = CH_3$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$

(XXVII) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$

(XXVIII) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = OCH_3$

4th The use of ultra-sonic radiation in the reaction between the compounds (XVIII), (XXVII) and (XXVIII) and the corresponding mercaptobenzimidazolic derivatives lead to the synthesis of the thioethers (XIX), (XXIX) and (XXX), at room temperature in five minutes with excellent yields.

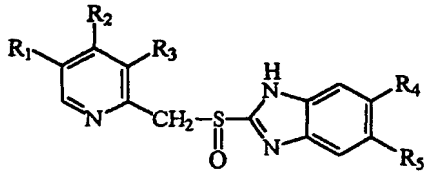


(XIX) $R_1 = CH_3$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$, $R_4 = OCH_3$, $R_5 = H$

(XXIX) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$, $R_4 = H$, $R_5 = H$

(XXX) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = OCH_3$, $R_4 = H$, $R_5 = OCHF_2$

5th The oxidation reaction of the thioethers (XIX), (XXIX) and (XXX) was investigated for the first time before the replacement of nitro, chloro, bromo and iodo groups by the methoxile group. This reaction was studied with several oxidizing agents such as *m*-chloroperoxybenzoic acid, oxone, magnesium salt of the monoperoxyphthalic acid and also hydrogen peroxide or *tert*-butyl hydroperoxide catalyzed by a rhenium or a vanadium compound, yielding the sulfoxides (XXII), (XXXI) and (XXXII) with good yields.



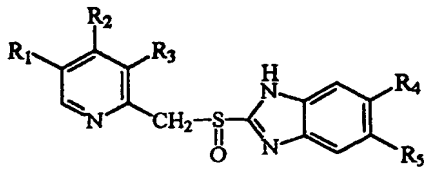
(XXII) $R_1 = CH_3$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$, $R_4 = OCH_3$, $R_5 = H$

(XXXI) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$, $R_4 = H$, $R_5 = H$

(XXXII) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = OCH_3$, $R_4 = H$, $R_5 = OCHF_2$

6th The substitution reactions of R_2 groups at 4 position of pyridine in the sulfoxides (XXII), (XXXI) and (XXXII) was achieved using the corresponding salts RO^-Na^+ at reflux temperature. These reactions were also performed in the presence of several catalysts, allowing the preparation of the omeprazole (XXI), lansoprazole (XXXIII) and pantoprazole (XXXIV) with moderate yields. The replacement of nitro, chloro,

bromo and iodo by the methoxile group after the oxidation of thioether has the advantage of allowing the preparation of omeprazole (XXI), lansoprazole (XXXIII) and pantoprazole (XXXIV) in basic conditions, without the problems related to the decomposition of these compounds, which normally take place in other processes described in the literature, involving acid conditions in the thiother oxidation.



(XXI) $R_1 = CH_3$, $R_2 = OCH_3$, $R_3 = CH_3$, $R_4 = OCH_3$, $R_5 = H$

(XXXIII) $R_1 = H$, $R_2 = OCH_2CF_3$, $R_3 = CH_3$, $R_4 = H$, $R_5 = H$

(XXXIV) $R_1 = H$, $R_2 = OCH_3$, $R_3 = OCH_3$, $R_4 = H$, $R_5 = OCHF_2$

This reaction sequence makes it possible to prepare these anti-ulcer compounds in a relatively simple and quick way and it is a good alternative to the previously reported methods.

EXAMPLES

Example 1: Oxidation of the pyridines

To a solution of 2,3,5-colidine (I) (2 g, 0.016 mol) in dichloromethane (10 ml) was added hydrogen peroxide 30% (5 eq.) and methyltrioxorhenium (MTO) (1.5% mol). After 3 hours in stirring at room temperature, it was added a aqueous solution of $NaHSO_3$ (10 ml). The two phases were separated and the aqueous phase was extracted with dichloromethane (3x50 ml). The organic phases were dried with anhydrous sodium sulfate and the solvent was evaporated, yielding a solid ($\eta = 91\%$).

Example 2: Nitration of the pyridine *N*-oxide

The suspension of claycop (240 mg) in acetic anidride (0.7 ml) was stirred at room temperature until the acquisition of a blue coulour (30 minutes). Then, it was added a solution of the 2,3,5-trimethylpyridine *N*-oxide (II) (69 mg, 0.5 mmol) in nitric acid fuming (0.5 ml). After 2 hours of stirring at room temperature, the mixture was filtered and the residue was washed with dichloromethane. The solution was neutralized with a aqueous solution of sodium hydroxide 10M and it was extracted with dichloromethane (3x50 ml). The organic phases were dried with anhydrous sodium sulfate and after the evaporation of the solvent, it was obtained the 2,3,5-trimethyl-4-nitropyridine *N*-oxide (III) as a yellow solid ($\eta = 87\%$).

Example 3: Chlorination of the 2-methylpyridines

It was added one-tenth of a solution of phosphoryl chloride (1.2 ml) in dichloromethane (10 ml) to a stirred solution of 2,3,5-trimethyl-4-nitropyridine *N*-oxide (III) (3g, 0.0165 mol) in dichloromethane (10 ml), under a nitrogen atmosphere. After one-tenth of the phosphoryl chloride solution had been added, simultaneously the addition of a solution of triethylamine (2.6 ml) in dichloromethane (10 ml) was begun. The rate of addition of the phosphoryl chloride and the triethylamine solutions was the same. After the addition of the phosphoryl chloride solution had been completed, the remaining one-tenth of the triethylamine solution was completed. After 15 minutes of stirring, the reaction mixture was neutralized with a solution of sodium

hydrogencarbonate and extracted with dichloromethane (3 x 50 ml). The organic phases were dried with sodium sulfate and after evaporation we obtained a oil, known as the 2-chloromethyl-3,5-dimethyl-4-nitropyridine (XVIII) (η = 91%).

Example 4: Reaction for thioethers formation

The solution of 5-methoxy-2-mercaptobenzimidazole (2.7g, 0.015 mol) and sodium hydroxide (1.2g, 2 eq.) in ethanol (20 ml) / H_2O (2 ml) was stirred at room temperature for 10 minutes. After the addition of the 2-chloromethyl-3,5-dimethyl-4-nitropyridine (XVIII) (3g, 0.015 mol), the reaction mixture was subjected to ultra-sonic radiation for 5 minutes. Then the reaction mixture was filtered, treated with norit and dried with sodium sulfate. After a new filtration and subsequent evaporation the thiother (XIX) was obtained, which was recristalized in methanol (η = 93%).

Example 5: Thioethers oxidation

To the solution of thioether (XIX) obtained in example 4th (5 g, 0.0145 mol) in dichloromethane (50 ml) at O °C, was added a solution of oxone (0.14g, 50 ml of water) and the reaction mixture was stirred at the temperature of 0-5 °C for 2 hours. The two phases were separated and the organic phase was extracted with water (2 x 50 ml). The organic phases were dried with sodium sulfate and evaporated. The sulfoxide (XXII) was precipitated with acetonitrile (η = 92%).

Example 6: Substitution of the nitro group by the methoxide group

A solution of sulfoxide (XXII), obtained in the 5th example (1 g, 2.78 mmol) in dichloromethane (20 ml) and the catalyst hexadecyltributylphosphonium bromide (0.1g, 0,1eq.) were added to a solution of sodium methoxide in methanol, prepared from 0.26 g of metallic Na and methanol (20 ml). After 4 hours of stirring at reflux temperature, the reaction mixture was evaporated and the solid was washed with dichloromethane (3x60 ml). The solution was treated with norit and evaporated. The obtained oil was crystallized in acetonitrile (η = 60%).

Bibliography

1- Arne Brandstrom, Bo Lamm, United States Patent 4,544,750, 1985.

2- Arne Brandstrom, European Patent 0103553 B1, 1989.

3- Alberto Palomo Coll, Spain Patent 2035767, 1993.

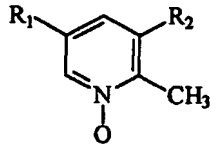
4- Karl Baumann, European Patent 369,208, 1990.

5- Karl Baumann, German Patent 3,840,372, 1990.

6- Alberto Palomo Coll, European Patent 0484265 A1, 1992.

We claim:

1st Process for the preparation of pyridines *N*-oxide (II), (XXIII), (XXIV) characterized by the use an oxidizing agent such as hydrogen peroxide or *tert*-butyl hydroperoxide, catalyzed by a rhenium compound.



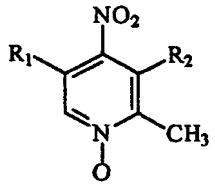
(II) $R_1 = CH_3$, $R_2 = CH_3$

(XXIII) $R_1 = H$, $R_2 = CH_3$

(XXIV) $R_1 = H$, $R_2 = OCH_3$

2nd Process for the pyridines oxidation according to the 1st claim, characterized by the use of a compound such as organotrioxorhenium, where the alkyl group may be methyl, ethyl, cyclopropyl or cyclopentadieneyl.

3rd Process for the preparation of nitro compounds (III), (XXV) and (XXVI) characterized by the use of nitric acid fuming at room temperature, in presence or absence of a claycop.

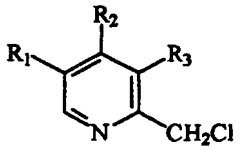


(III) $R_1 = CH_3$, $R_2 = CH_3$

(XXV) $R_1 = H$, $R_2 = CH_3$

(XXVI) $R_1 = H$, $R_2 = OCH_3$

4th Process for the preparation of the compounds with the formulas (XVIII), (XXVII) and (XXVIII), characterized by the use of the reaction system $POCl_3$ / Et_3N.

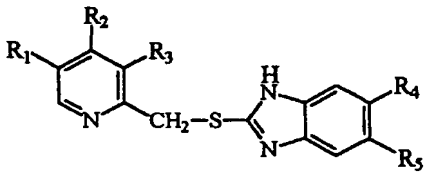


(XVIII) $R_1 = CH_3$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$

(XXVII) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$

(XXVIII) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = OCH_3$

5th Process for the preparation of the thioethers with the formulas (XIX), (XXIX) and (XXX) by reaction between the substituted 2-chloromethylpyridines (XVIII), (XXVII) and (XXVIII) and the corresponding mercaptobenzimidazolic derivatives, characterized by the application of ultra-sonic and micro-wave radiation.

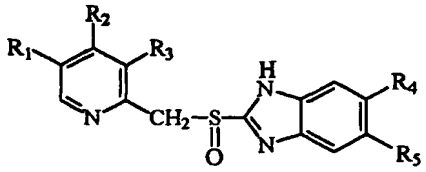


(XIX) $R_1 = CH_3$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$, $R_4 = OCH_3$, $R_5 = H$

(XXIX) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$, $R_4 = H$, $R_5 = H$

(XXX) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = OCH_3$, $R_4 = H$, $R_5 = OCHF_2$

6th Process for the preparation of the sulfoxides with the formulas (XXII), (XXXI) and (XXXII), characterized by the oxidation of the thioethers (XIX), (XXIX) and (XXX).



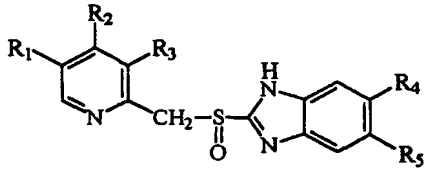
(XXII) $R_1 = CH_3$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$, $R_4 = OCH_3$, $R_5 = H$

(XXXI) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = CH_3$, $R_4 = H$, $R_5 = H$

(XXXII) $R_1 = H$, $R_2 = NO_2$, Cl, Br, I, $R_3 = OCH_3$, $R_4 = H$, $R_5 = OCHF_2$

7th Process for the oxidation of the thioethers (XIX), (XXIX) and (XXX) according to the 6th claim, characterized by the use of one of the following oxidizing agents: *m*-chloroperoxybenzoic acid, magnesium salt of the monoperoxyphthalic acid, oxone, hydrogen peroxide and *tert*-butyl hydroperoxide catalyzed by an alkylrhenium or a vanadium compound.

8th Process for the preparation of omeprazole (XXI), lansoprazole (XXXIII) and pantoprazole (XXXIV), characterized by the substitution reaction of the nitro, chloro, bromo and iodo groups at 4-positions of the pyridine in the sulfoxides (XXII), (XXXI) and (XXXII), catalyzed by a RO^-Na^+ salt.



(XXI) $R_1 = CH_3$, $R_2 = OCH_3$, $R_3 = CH_3$, $R_4 = OCH_3$, $R_5 = H$

(XXXIII) $R_1 = H$, $R_2 = OCH_2CF_3$, $R_3 = CH_3$, $R_4 = H$, $R_5 = H$

(XXXIV) $R_1 = H$, $R_2 = OCH_3$, $R_3 = OCH_3$, $R_4 = H$, $R_5 = OCHF_2$

9th Process for the preparation of omeprazole (XXI), lansoprazole (XXXIII) and pantoprazole (XXXIV) according to the 8th claim, characterized by the application of a catalytic quantity of a quaternary salt of ammonium or phosphonium or a crown ether.

10th Process for the preparation of omeprazole (XXI), lansoprazole (XXXIII) and pantoprazole (XXXIV) according to the 8th claim, characterized by the use of basic conditions.

INTERNATIONAL SEARCH REPORT

PCT/IB 00/01057

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/89 C07D213/61 C07D213/65 C07D401/12 C07B43/02
C07B41/00 C07B39/00 A61K31/4439 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07B A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	C. COPÉRET: "A Simple and Efficient Method for the Preparation of Pyridine N-Oxides" JOURNAL OF ORGANIC CHEMISTRY, vol. 63, 1998, pages 1740-1741, XP002151456 Equation 1	1,2
X	US 5 670 526 A (NISHI TAKAO ET AL) 23 September 1997 (1997-09-23) column 25, line 24 - line 34	3
	-/—	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2000	16/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	M.J. TANGA: "Synthesis of Five Potential Heterocyclic Amine Food Mutagens" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 34, 1997, pages 717-727, XP002151457 page 723, paragraph 4	3
Y	M.L. ASH: "The Synthesis of 2-Chloromethylpyridine from 2-Picoline-N-Oxide" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 18, 1981, pages 939-940, XP002151458 Scheme 1	4
Y	EP 0 484 265 A (GENESIS PARA LA INVESTIGACION ;ESTEVE QUIMICA SA (ES)) 6 May 1992 (1992-05-06) cited in the application page 13, line 36 - line 50 examples 4,12	4
X	example 13	5
X	example 28	6,7
X	example 18	8

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